

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY**

BRISTOL-MYERS SQUIBB COMPANY,

Plaintiff,

v.

APOTEX, INC., and
APOTEX CORP.

Defendants.

Civil Action No. 3:10-cv-05810 (MLC)(LHG)

Electronically Filed Under Seal

PLAINTIFF'S RESPONSIVE CLAIM CONSTRUCTION BRIEF

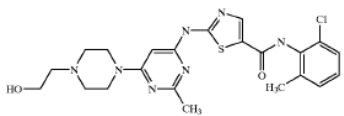
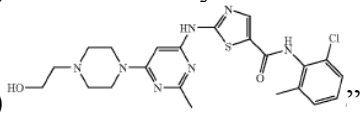
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Plaintiff Bristol-Myers Squibb Company (“BMS”) respectfully provides its Responsive Claim Construction Brief in support of its proposed construction of certain terms of U.S. Patent Nos. 6,596,746 (“the ‘746 patent”), 7,125,875 (“the ‘875 patent”), 7,153,856 (“the ‘856 patent”) and 7,491,725 (“the ‘725 patent”).

I. INTRODUCTION

It is clear from Apotex’s opening brief that its proposed constructions find little or no support in the intrinsic evidence. Rather, the proposed constructions consist mainly of mere attorney arguments and are often contradicted by the clear testimony of Apotex’s own experts. For example, Apotex asserts that “if this Court seeks to construe the chemical language [of claim 6 of the ‘746 patent], it can simply instruct that the claim 6 chemical nomenclature as having its plain and ordinary meaning, according to standard IUPAC nomenclature guidelines, *and further note that the term excludes dasatinib.*” (Dkt. 63, Apotex’s Opening Claim Construction Brief (hereinafter “Apotex Br.”) at 10-11 (emphasis added).) This directly contradicts Apotex’s expert Dr. Fernandez’s admission that one of ordinary skill would understand the chemical name at issue in claim 6 is in fact dasatinib. (Certification of Christine I. Gannon in Support of Plaintiff’s Responsive Claim Construction Brief (hereinafter “Gannon Cert. II”) Ex. A, Fernandez Dep. 44:5-24, May 15, 2012 (“That name appears to be, indeed, that of dasatinib.”)). Apotex further asserts that the chemical structure in claim 1 of the ‘746 patent is not dasatinib because of the omission of two hydrogen atoms on the drawn structure. However, Dr. Fernandez’s own published patent application uses the exact same accepted convention of omitting hydrogens from amines and amides when drawing a chemical structure. (*Id.* at 107:2-109:14; Gannon Cert. II Ex. C, Plaintiff’s Dep. Ex. 17 at p. 3.)

Respecting the ‘725 patent, Apotex’s expert Dr. Desiraju testified that “substantially in accordance” does not mean “must match,” contradicting the position urged by Apotex. (Gannon

Cert. II Ex. D, Desiraju Dep. 79:6-10, May 9, 2012.) Instead, Dr. Desiraju testified that “substantially in accordance” means the same as “matches well,” which is nearly identical to BMS’s proposed construction of “substantially identical.” (*Id.* at 60:3-16.) And he has no problem concluding that the two X-ray diffraction patterns in FIG. 1 of the ‘725 patent match well and thus are “substantially in accordance” with each other. (*Id.* at 60:3-24.)

Apotex contends that the ‘725 patent does not provide the measurement protocols for the differential scanning calorimetry (DSC) studies used to obtain the data depicted in FIG. 2 and recited in the claims. (Apotex Br. at 30.) But once again its position is belied by Dr. Desiraju who testified that the descriptions in the ‘725 patent were sufficient for one of ordinary skill in the art to conduct the disclosed DSC studies and thermogravimetric analyses (TGA). (Gannon Cert. II Ex. D, Desiraju Dep. 105:6-106:2.) Finally, Apotex argues the term “substantially pure” is indefinite. (Apotex Br. at 24 (citing Desiraju ¶ 74).) However, Dr. Desiraju conceded that a person of ordinary skill in the art would understand the meaning of “substantially pure” in the context of the patent. (Gannon Cert. II Ex. D, Desiraju Dep. 128:6-130:11.)

Having no viable non-infringement or invalidity positions based on proper constructions of the claims, Apotex resorts to refusing to construe many claim terms and arguing instead that these terms are indefinite often based purely on attorney arguments. Apotex also improperly attempts to import the scope of the asserted claims into its proposed constructions rather than simply construing the claim terms as required under the Federal Circuit’s *en banc* decision *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005). BMS respectfully submits the Court should not be persuaded by Apotex’s misguided approaches, and should adopt BMS’s constructions -- which closely align with the ordinary meaning of the claim terms and the patents’ teachings.

II. CONSTRUCTION OF TERMS IN THE ‘746, ‘875, AND ‘856 PATENTS

A. “A compound or salt thereof selected from the group consisting of”

The phrase “[a] compound or salt thereof selected from the group consisting of” appears in claim 6 of the ‘746 patent, which is directed to a compound or salt selected from a list of compounds that includes dasatinib. BMS’s construction is “[p]lain meaning as understood by a person of ordinary skill in the art. ‘Salt’ denotes acidic and/or basic salts formed with inorganic and/or organic acid and bases. In addition, ‘selected from the group consisting of’ is a well accepted form of alternative expression commonly referred to as a Markush group. Thus, any pharmaceutical composition containing a compound listed in this claim would fall within the scope of the claim.” (Dkt. 62, BMS’s Opening Claim Construction Brief (hereinafter “BMS Br.”) at 5.)

Instead of construing the entire claim term as agreed upon in the March 2, 2012 Joint Claim Construction and Prehearing Statement (Dkt. 51), Apotex seeks to construe this term piecemeal by providing separate definitions for “compound” and “salt.” Apotex asserts the term “compound” “encompasses ‘salts’; prodrugs and solvates of the compound[]”; and ‘stereoisomers of the ... compound[].’” (Apotex Br. at 5-6.) In support of this construction, Apotex relies on the statement in ‘746 patent that “[p]rodrugs and solvates of the compounds of the invention are also contemplated herein.... All stereoisomers of the present compounds ... are contemplated within the scope of this *invention*.” (*Id.* at 5 (emphasis added).) However, Apotex erroneously equates what is described as within the scope of the “invention” with the definition of “compound.” A prodrug, solvate, salt or stereoisomer of a compound may be covered by claim 6, but these terms do not constitute definitions of a “compound.”

As Apotex points out, the ‘746 patent states “[p]rodrugs and solvates *of the compounds* of the invention” and “stereoisomers *of the present compounds*” are contemplated within the scope

of the invention. (Dkt. 62-3, Declaration of Dr. William L. Jorgensen (hereinafter “Jorgensen”) Ex. A, col. 7, ll. 1-12 (emphasis added).) The ‘746 patent is merely describing the forms of compounds that may be covered by the claims, not defining the term “compound.” Apotex has not advanced a proper claim construction argument, but rather has made arguments regarding the scope of the asserted claims, which should be addressed at a later time with respect to infringement or validity of the patents-in-suit, not during claim construction.

With respect to the term “salt,” the ‘746 patent defines salt as “acidic and/or basic salts formed with inorganic and/or organic acids and bases.” (Jorgensen Ex. A, col. 6, ll. 21-23.) BMS does not dispute that the ‘746 patent states zwitterions “may be formed” and that quaternary ammonium salts are included within the term “salt.” (*Id.* at col. 6, ll. 23-27.) However, zwitterions and quaternary ammonium salts are examples of “acidic and/or basic salts formed with inorganic and/or organic acids and bases.” (Supplemental Declaration of Dr. William L. Jorgensen (hereinafter “Jorgensen Suppl.”) ¶ 12.)

Apotex’s apparent assertion that the term “compound” should always be defined to include a salt is incorrect. This construction is inconsistent with the very text of claim 6 which states “a compound *or* salt thereof selected from the group consisting of.” (Emphasis added.)

Apotex next argues that the term “a compound or salt thereof selected from the group consisting of” “precludes mixtures of the listed compounds and other compounds not part of the list, including impurities.” (Apotex Br. at 7.) As discussed in BMS’s opening brief, this assertion directly contradicts well established authority holding that “consisting of” *does not* exclude impurities. (See BMS Br. at 7.) Further, the claim language “group consisting of” does not preclude the claimed compound from being combined with other substances outside the Markush group as expressly described in the ‘746 patent. (Jorgensen Ex. A, col. 25, ll. 27-35.)

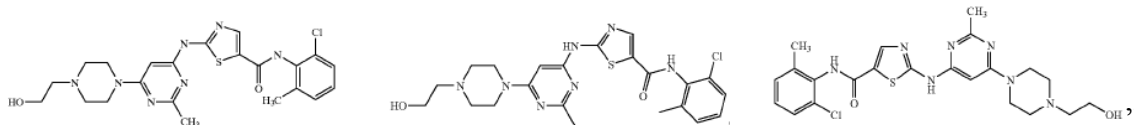
The “selected from the group consisting of” language merely restricts the selection of the “compound or salt thereof” to those enumerated in claim 6, but does not dictate the manner in which the “compound or salt thereof” is combined with other substances outside the Markush group, for instance in a pharmaceutical composition. *See Teva Pharm. USA Inc. v. Amgen, Inc.*, 2010 U.S. Dist. LEXIS 95288, at *20-21 (E.D. Pa. Sep. 10, 2010) (rejecting construction that use of a Markush group means that “there can be only one member of the Markush group present in a product, and, if there are more, then the product is outside the scope of the patent”).

Apotex erroneously relies on *Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 334 F.3d 1274, 1280-81 (Fed. Cir. 2003) to support its flawed reasoning. In *Abbott*, the claim at issue was directed to a *composition* comprising, among others, a Lewis acid selected from the group consisting of several possibilities. *Id.* at 1276. The *Abbott* court stated that use of “‘a’ with ‘consisting of’ ... indicates only one member of a Markush group,” *i.e.*, mixing or combining members of the Markush group is not permitted. *Id.* at 1281. That case has nothing to do with whether impurities are excluded by the use “consisting of” in a claim directed to a *compound* or whether the claimed compound can be combined with other ingredients in a composition.

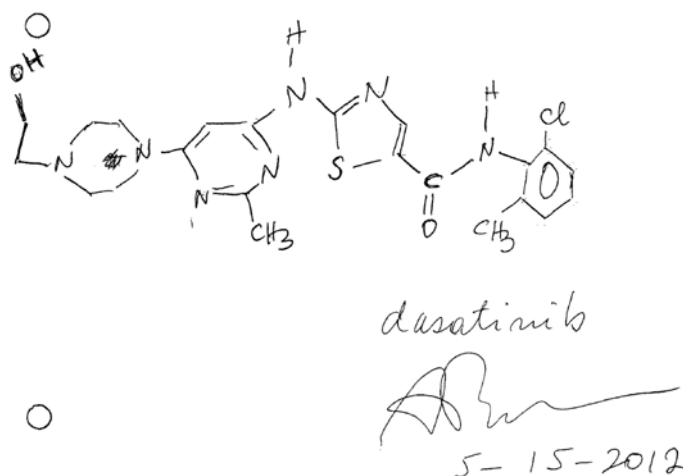
Accordingly, BMS respectfully submits that its proposed construction should be adopted.

B. Chemical names identified in claim 6 including but not limited to “N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino-5-thiazolecarboxamide.”

The chemical name “N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino-5-thiazolecarboxamide” is one of the names listed in the Markush group in claim 6 of the ‘746 patent. BMS’s proposed construction is “N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide represents the compound having the following equivalent chemical structures:



BMS's proposed construction is consistent with the plain meaning of the chemical name as understood by one of ordinary skill in the art, and in fact it was confirmed by Apotex's own expert Dr. Fernandez. Dr. Fernandez admitted that the chemical name recited in claim 6 follows the IUPAC guidelines.¹ (Gannon Cert. II Ex. A, Fernandez Dep. 48:10-15.) He further testified that the recited name is the name for dasatinib. (*Id.* 44:5-24 ("That name appears to be, indeed, that of dasatinib")). In fact, when asked to draw the compound associated with that chemical name Dr. Fernandez drew the structure for the dasatinib compound. (*Id.* at 44:5-47:24; Gannon Cert. II Ex. B, Plaintiff's Dep. Ex. 9.)



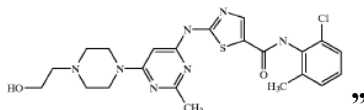
This directly contradicts Apotex's assertion that "if this Court seeks to construe the chemical language, it can simply instruct that the claim 6 chemical nomenclature as having its

¹ The IUPAC guidelines are not the only way in which a compound can be named. (*See* Jorgensen ¶¶ 14, 15, 20, 22.) When asked to identify specific portions of the IUPAC guidelines he is relying on to render his opinions in this case, Dr. Fernandez could not do so and instead stated his opinion was based on the "entire document" and the "intent" of the document. (Gannon Cert. II Ex. A, Fernandez Dep. 55:2-15.)

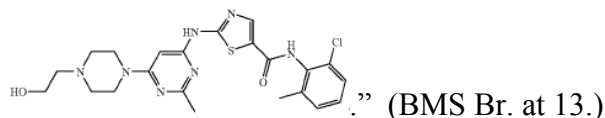
plain and ordinary meaning, according to standard IUPAC nomenclature guidelines, *and further note that the term excludes dasatinib.*” (Apotex Br. at 10-11 (emphasis added).)

Since the three chemical structures in BMS’s proposed construction all correspond to the chemical name in claim 6 and are all structures of dasatinib (BMS Br. at 7-8, 13-14; Jorgensen Suppl. ¶¶ 7-8.), BMS respectfully submits that its proposed construction should be adopted.

C. “The compound



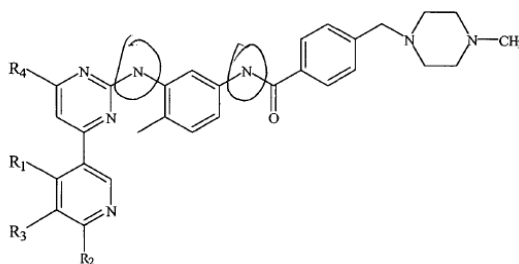
This phrase appears in claim 43 of the ‘746 patent and claim 1 of the ‘856 patent and is directed to the compound known as dasatinib. BMS’s proposed construction is “[t]he compound represented by ‘N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, and is the same as



Apotex asserts the structure in claim 43 “cannot represent a compound known as dasatinib.” (Apotex Br. at 11-13.) However, the chemical structure of claim 43 of the ‘746 patent and claim 1 of the ‘856 patent is represented by the chemical name ‘N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide as specifically disclosed in Example 455 and as recognized by Apotex’s expert Dr. Fernandez. (Gannon Cert. II Ex. A, Fernandez Dep. 53:3-54:9; Jorgensen, ¶ 11.) As discussed above, Dr. Fernandez admitted that this chemical name is “*that of dasatinib.*” (Gannon Cert. II Ex. A, Fernandez Dep. 44:5-24.) Further, Dr. Fernandez conceded that even under his own construction dasatinib would be encompassed within the scope of claim 43. (*Id.*, 106:2-19.)

Importantly, a “person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification.” *Phillips*, 415 F.3d at 1313. Further, “[i]t is a well-established axiom in patent law that a patentee is free to be his or her own lexicographer and thus may use terms in a manner contrary to or inconsistent with one or more of their ordinary meanings.” See *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). Thus, it is clear to one of ordinary skill, and indeed, to Apotex’s expert, that when reading the claim in light of the patent the compound in claim 43 is dasatinib.

Apotex’s assertion that this compound cannot be dasatinib due to the omission of two hydrogen atoms on the structure has no merit. As explained by Dr. Jorgensen, it is an acceptable convention in the field of chemistry to omit the hydrogen of amines and amides when drawing a chemical structure, and a person of ordinary skill would understand that in the structure shown in claim 43, the nitrogen of the amine and the nitrogen of the amide are bonded to a hydrogen. (Jorgensen ¶¶ 17-19; Jorgensen Suppl. ¶¶ 4-6.) In fact, this acceptable convention was used in Apotex’s expert Dr. Fernandez’s own published patent application, in which the hydrogen atoms were omitted from two bridging nitrogens (circled below by Dr. Fernandez) in the chemical formula below. (Gannon Cert. II Ex. A, Fernandez Dep. 107:2-109:14; Gannon Cert. II Ex. C, Plaintiff’s Dep. Ex. 17; Jorgensen Suppl. ¶¶ 9-11.)



Formula 1

Further, as conceded by Dr. Fernandez, all of the specific compounds disclosed and claimed in his patent and covered by this formula have a hydrogen bonded to the two bridging nitrogens. (Gannon Cert. II Ex. A, Fernandez Dep. 119:7-123:25.) Thus, it is abundantly clear that one of ordinary skill in the art would understand that the hydrogen need not be explicitly shown on nitrogens.

In addition, as explained by Dr. Jorgensen, chemical drawing and naming software programs such as ChemDraw treat chemical structures with or without hydrogens explicitly drawn on nitrogens of amines and amides as the same and would generate the same name for both. (Jorgensen Suppl. ¶¶ 3-6.)

Accordingly, BMS respectfully submits that its proposed construction should be adopted.

D. “administering to” and “administering orally to”

The phrases “administering to” and “administering orally to”² appear in claims 7, 44 and 47 of the ‘746 patent, claim 1 of the ‘856 patent, and claims 1, 2, 3, 11, and 27 of the ‘875 patent. BMS’s proposed construction is “[t]o mete out or dispense or to give remedially.” (BMS Br. at 9.)

Apotex asserts the term “administering to” requires two actors - the administering actor and the receiving actor -- as construed by “examin[ing] principally the claim language and any syntactic signs of its meaning.” (Apotex Br. at 16.) Apotex failed to cite a single case construing the term “administering to” as requiring two actors. Rather, Apotex cites *Eastman Kodak Co. v. Goodyear Tire & Rubber Co.*, 114 F.3d 1547 (Fed. Cir. 1997) for the proposition that one must construe “to” by examining any syntactic signs of its meaning. (Apotex Br. at 16.) Apotex’s argument is flawed. The only verb in the method claims is “administering” and only a

² The additional proposed construction language corresponding to “orally” is contained in brackets in both parties proposed constructions.

single actor is required to perform that act. “To” is a preposition indicating the direction of said action, which in this case is toward the indirect object, the “subject in need thereof.” The “subject in need thereof” is not required by the claim to undertake any action according to the claim language or the patent specification. However, the “subject in need thereof” can be the actor and administer the claimed compound to himself, requiring only one actor.

In addition, as stated in BMS’s opening brief, the Court in *Acorda Therapeutics Inc. v. Apotex Inc.*, 2011 WL 4074116, at *27 (D.N.J. 2011), stated that given its construction of “administering,” which is nearly identical to BMS’s proposed construction, “a physician, pharmacist, or patient could alone infringe the patent.” (BMS Br. at 10.) No two actors are required.

Apotex also contends that two actors are required because the “specification envisions a treatment population that includes animals, who cannot administer drugs to themselves.” Again, since the claim language does not require the “subject in need thereof” to perform any acts, this differentiation is inapposite. A caretaker such as a veterinarian can alone administer the compound to an animal. Thus, for all the reasons stated, Apotex’s construction of “administering to” should be rejected.

E. “a subject in need thereof”

The phrase “a subject in need thereof” appears in claims 7, 44, and 47 of the ‘746 patent, claim 1 of the ‘856 patent, and claims 1, 2, 3, 11, and 27 of the ‘875 patent. BMS’s proposed construction is “[a]n animal, including a human, in need thereof.”

Relying on *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329 (Fed. Cir. 2003) and *Schering Corp v. Glenmark Pharm. Inc.*, 2008 WL 4307189 (D.N.J. Sept. 16, 2008), Apotex erroneously asserts that “the phrase ‘a subject in need thereof’ requires both a subject and a person who has diagnosed that subject as ‘in need thereof’.” (Apotex Br. at 13.) In construing “in need of such

treatment,” the *Schering* Court cited the Federal Circuit’s holding in *Jansen* that “said term included the [direct] infringer’s intent to use the drug for its intended purpose.” *Schering*, 2008 WL 4307189, at *9 (citing *Jansen*, 342 F.3d at 1334). Neither court read into the term a requirement of a second person to diagnose the subject as “in need thereof.” The term “in need thereof” includes the direct infringer’s intent, not the origination of the intent. As long as the direct infringer intends to use the drug for its intended purpose, it does not matter how he developed that intent. Further, there is nothing in the specification of the patents-at-issue that requires a diagnosis step.

Apotex also argues that the claim language requires the step of “administering to” a subject “in need thereof” and that this means that two people are needed to perform the method of treatment. (Apotex Br. at 14-15.) Notably, Apotex fails to identify any support for the addition of this “second party” limitation in the specification or the prosecution histories. Apotex’s argument is flawed because the only act being performed is “administering” and only one individual is needed to perform this act. The “subject in need thereof” is not an actor in the context of the claim. For all these reasons, Apotex’s proposed construction requiring “two actors” should be rejected.

Finally, Apotex’s proposed construction of “any living organism” is much broader than how the term is defined in the ‘746 patent and is therefore improper. (*Id.* at 15.) As recognized by Apotex, the patent states that “[p]referred subjects for treatment include *animals*, most preferably mammalian species such as humans, and domestic animals such as dogs, cats and the like” (*Id.* at 13; Jorgensen Ex. A, col. 26, ll. 53-57 (emphasis added).) Accordingly, given the clear intrinsic record, “a subject in need thereof” should be construed as “an animal, including a human, in need thereof.”

F. “wherein the cancer is resistant to treatment by STI-571” or “wherein the chronic myelogenous leukemia (CML) is resistant to STI-571”

This phrase appears in claims 9, 10, 12 and 27 of the ‘875 patent. These claims are directed to methods of treating cancer with compounds of formula III or formula IV wherein the cancer is resistant to treatment by STI-571. BMS’s proposed construction is “[w]herein the cancer [or chronic myelogenous leukemia (CML)] exhibits resistance to treatment by STI-571.”

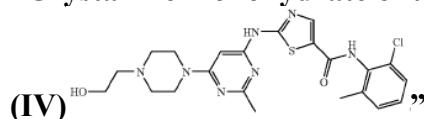
Apotex asserts that this term “must be construed to require both a subject in need of cancer treatment and a second person who has diagnosed the cancer as resistant to STI-571.” (Apotex Br. at 17.) Apotex’s line of reasoning is the same as the one it presented for the term “subject in need of.” As stated in section II.E for the term “subject in need of,” there is nothing in the claim, specification, or prosecution history that requires a diagnosing step. And Apotex again cites *Jansen* and *Schering* in support of its argument; however, these cases stand only for the position that the claim has to be interpreted to require the method be practiced with the intent to achieve the objective stated in the preamble -- they do not read a diagnosing step into the claim. Thus, Apotex’s construction should be rejected.

BMS’s proposed construction on the other hand is supported by the specification and the accepted meaning of the term. The ‘875 patent discloses that the claimed compounds may be useful “in the treatment of cancers that are sensitive to and resistant to chemotherapeutic agents that target BCR-ABL and c-KIT, such as, for example, Gleevec[®] (STI-571).” (Jorgensen Ex. C, col. 28, ll. 26-38.) The term “resistant” is defined in the dictionary as “giving or capable of resistance.” Merriam-Webster’s Collegiate[®] Dictionary 1564 (Deluxe ed. 1998) (Dkt. 62-2, Certification of Christine I. Gannon in Support of Plaintiff’s Opening Claim Construction Brief (hereinafter “Gannon Cert.”) Ex. F). Accordingly, the Court should construe this claim

consistent with the construction set forth by BMS -- “wherein the cancer [or chronic myelogenous leukemia (CML)] exhibits resistance to treatment by STI-571.”

III. CONSTRUCTION OF TERMS IN THE ‘725 PATENT

A. “Crystalline monohydrate of the compound of formula



This phrase appears in claims 1, 3 and 12. These claims are directed to a crystalline monohydrate of the compound of formula IV. BMS’s proposed construction is plain meaning as understood by a person of ordinary skill in the art, *i.e.*, the monohydrate of the compound of formula (IV) in a crystalline form.

Apotex asserts that the term “crystalline monohydrate of the compound of formula (IV)” should be construed to mean a “raw material” produced by the process conditions presented in the specification.³ (Apotex Br. at 21-23.) There is nothing in the intrinsic record that limits the crystalline monohydrate of the compound of formula (IV) to a raw material made by the process conditions presented in the specification. Apotex points only to its expert Dr. Desiraju’s bare statement that “[i]t is clear from reviewing the ‘725 patent that the claimed ‘crystalline monohydrate of the compound of Formula (IV)’ is the form of the raw material that resulted from the process conditions taught in Example 8.” (Dkt. 63-5, Declaration of Dr. Gautam Desiraju (hereinafter “Desiraju”) ¶ 25.)

³ Apotex appears to suggest an earlier application’s specification, rather than the current specification for the ‘725 patent, is relevant for claim construction. (Apotex Br. at 20.) This is improper. *See Sun Pharm. Indus., Ltd. v. Eli Lilly & Co.*, 611 F.3d 1381, 1388 (Fed. Cir. 2010) (“Instead, *Phillips* makes clear that claim terms must be construed in light of the entirety of the patent, including its specification, and that the specification to be consulted is that of the issued patent, not an earlier application ... [T]he relevant specification for claim construction purposes is that of the issued patent, not an early version of the specification that may have been substantially altered throughout prosecution.”).

However, Apotex's construction is belied by Dr. Desiraju's own testimony. He conceded that the term "raw material" does not appear in any of the claims of the '725 patent and the claims say nothing about limiting the crystalline monohydrate to the process conditions. (Gannon Cert. II Ex. D, Desiraju Dep. 45:7-10.) Dr. Desiraju defined "raw material" as "what is obtained when you do [the process of] Example 8." (*Id.* at 44:14-45:6.) But he conceded that the '725 patent states that Example 8 is "[a]n *example* of the crystallization procedure to obtain the crystalline monohydrate form..." (*Id.* at 46:19-47:3 (emphasis added).) He further acknowledged that Example 8 itself discloses five other alternate methods of making the monohydrate and he stated that all of them seem suited to make the monohydrate. (*Id.* at 47:4-22.) He also conceded that he did not perform any experimental work to see whether the claimed monohydrate could be made by a procedure other than Example 8. (*Id.* at 48:5-11.) He did, however, concede that in the course of his own research, a crystalline polymorph can frequently be made by different processes. (*Id.* at 49:15-21.) Dr. Desiraju goes on to expand his definition of the "crystalline monohydrate of the compound of formula (IV)" by not restricting it to "raw material" and including anything that is crystalline, including single crystals. (*Id.* at 52:16-22.) Thus, Apotex's construction for "crystalline monohydrate of the compound of formula (IV)" is not supported, but rather is thoroughly contradicted, by the testimony of its own expert.

Apotex erroneously relies on *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282 (Fed. Cir. 2009) to support its flawed construction. As the Federal Circuit stated in *Abbott*, "this court has expressly rejected the contention that if a patent describes only a single embodiment, the claims of the patent must be construed as being limited to that embodiment." *Id.* at 1290 (quoting *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 906 (Fed. Cir. 2004). *See also AFG Indus. v. Cardinal IG Co.*, 375 F.3d 1367, 1372-73 (Fed. Cir. 2004) (ruling it is improper to adopt a

construction “that would impermissibly import a process limitation into a pure product claim”). In *Abbott*, the Court limited the patent to Crystal A because “the rest of the intrinsic evidence, including the prosecution history and the priority [] application, evince a clear intention to limit the patent....” *Abbott*, 566 F.3d at 1290. No such intrinsic evidence exists here.

Accordingly, the Court should reject Apotex’s proposed construction and adopt BMS’s proposed construction.

B. “wherein the compound is substantially pure”

This phrase appears in claims 8, 15 and 16. BMS’s proposed construction is “[t]he compound itself having a purity greater than 90%. The ‘substantially pure’ compound may be employed in pharmaceutical compositions to which other desired components are added, for example, excipients, carriers, or active chemical entities of different molecular structure.” (BMS Br. at 26.)

Instead of providing a construction, Apotex argues this term is indefinite because the unit of the purity is not specified. (Apotex Br. at 24 (citing *Desiraju* ¶ 74).). However, Dr. Desiraju conceded that a person of ordinary skill in the art would understand the meaning of “substantially pure” in the context of the patent. (Gannon Cert. II Ex. D, *Desiraju* Dep. 128:6-131:8.) Further, as Dr. Atwood stated in his supplemental declaration, the ‘725 patent would have taught one of ordinary skill in the art that the purity of the crystalline monohydrate of the compound of formula (IV) be measured by weight percent. (Supplemental Declaration of Dr. Jerry Atwood (hereinafter “Atwood Suppl.”) ¶¶ 7-12.)

Moreover, as stated in BMS’s opening brief, the use of terms such as “pure” or “substantially pure” to describe compounds is common and permitted under the law. *See In re Kratz*, 592 F.2d 1169, 1173-74 (C.C.P.A. 1979); *Evans Medical Ltd. v. American Cyanamid Co.*, 215 F.3d 1347, 1999 WL 594310, at * 5-6 (Fed. Cir. 1999); *Ortho-McNeil, Inc. v. Mylan Labs.*,

Inc., 348 F. Supp. 2d 713, 729-30 (N.D. W.Va. 2004), *aff'd*, 161 Fed. Appx. 944 (Fed. Cir. 2005). Thus, Apotex's indefiniteness argument should be rejected.

BMS's proposed construction on the other hand is expressly supported by the specification. (BMS Br. at 26.) Accordingly, BMS submits that its proposed construction should be adopted.

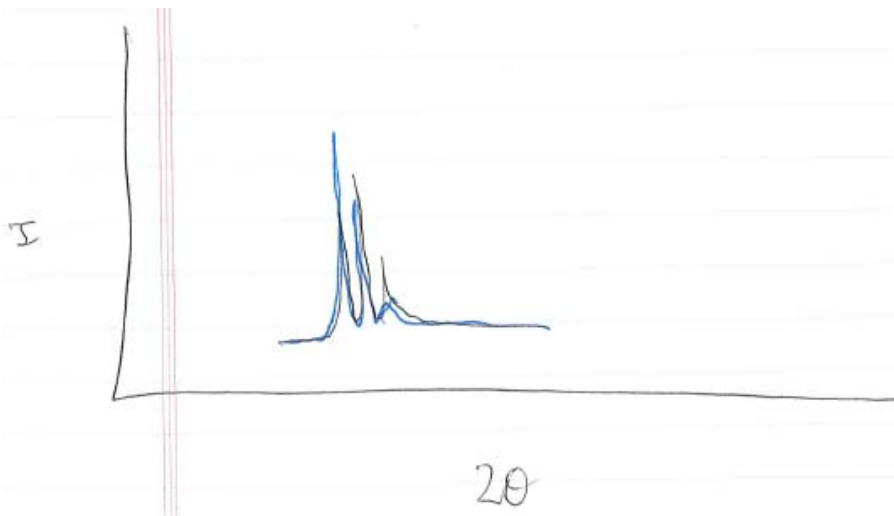
C. “which is characterized by an X-ray powder diffraction pattern substantially in accordance with that shown in FIG. 1”

This phrase appears in claim 1. BMS's proposed construction is “which is characterized by an x-ray powder diffraction pattern that is substantially identical to those shown in FIG. 1 taking into account variations due to measurement errors and dependent upon the measurement conditions employed, but not taking into account the exact order of intensity of the peaks. The ability to ascertain substantial identities of X-ray diffraction patterns is within the purview of one of ordinary skill in the art.” (BMS Br. at 19.)

Apotex argues this term be construed as “the product being characterized *must match* the x-ray powder diffraction pattern presented in FIG. 1 of the patent specification, and further do so in such a way so as to uniquely identify the referenced ‘crystalline monohydrate of formula (IV).’” (Apotex Br. at 26-27 (emphasis added).) Apotex's proposed construction not only finds no support in the intrinsic record, it is directly contradicted by its expert Dr. Desiraju. Dr. Desiraju testified that “substantially in accordance” does not mean “must match.” (Gannon Cert. II Ex. D, Desiraju Dep. 79:6-10.) Instead, he offers a construction of “substantially in accordance” that is nearly the same as BMS's proposed construction of “substantially identical.” Dr. Desiraju testified that “substantially in accordance” means the same as “matches well.” (*Id.* at 60:3-16.) In fact, Dr. Desiraju has no problem concluding that the two X-ray diffraction patterns in FIG. 1 of the '725 patent match well and thus are “substantially in accordance” with

each other even though they are not identical. (*Id.* at 60:3-24.) Thus, Dr. Desiraju's testimony is in harmony with the teaching of the '725 patent that the ability to ascertain substantial identities of X-ray diffraction patterns is within the purview of one of ordinary skill in the art. (BMS Br. at 19-20.)

Dr. Desiraju further agrees that there are measurement errors associated with X-ray powder diffraction measurements and that it is not out of the ordinary to find two patterns that are not identical and yet they came from the same crystalline form. (*Gannon Cert. II Ex. D, Desiraju Dep.* 74:21-76:4; 94:25-97:13.) Dr. Desiraju also agrees with the '725 patent's teachings that in comparing X-ray diffraction patterns of different samples to determine whether they came from the same crystalline form, the "intensity need not be the same." (*Id.* at 93:16-94:17.) In fact, Dr. Desiraju illustrated an example of two X-ray diffraction patterns having different intensities (y-axis), but representing the same crystalline material. (*Id.* at 77:2-78:18; *Gannon Cert. II Ex. E, Plaintiff's Dep. Ex. 4.*)



Accordingly, BMS's proposed construction is supported by the intrinsic record, as well as by Apotex's own expert.

In his declaration, Dr. Desiraju opined that “[i]n order to positively identify an unknown sample of a compound as a hydrate of a compound using *only* X-ray powder diffraction, the X-ray powder diffraction patterns must match a qualified reference standard in such a way that the unknown sample can be uniquely identified....” (Desiraju ¶ 33.) (Emphasis added.) In his deposition, however, Dr. Desiraju admitted that the ‘725 patent has nothing to do with identifying unknown samples. The claims *require* that the substance being characterized is a crystalline monohydrate of the compound of formula (IV). (Gannon Cert. II Ex. D, Desiraju Dep. 82:23-83:11; 92:15-19.) In addition, the ‘725 patent discloses characterizing the crystalline monohydrate by various means, including X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA). (Dkt. 62-1, Declaration of Dr. Jerry Atwood (hereinafter “Atwood”) Ex. A, col. 44, l. 23 - col. 45, l. 31.) Dr. Desiraju agrees that all of these tests can be used to characterize a substance known to be a crystalline monohydrate of the compound of formula (IV). (Gannon Cert. II Ex. D, Desiraju Dep. at 87:22-90:5.) Thus, Dr. Desiraju understood the claim term in the context of the ‘725 patent.

Apotex cites *Roche Palo Alto LLC v. Ranbaxy Labs, Ltd.*, 2009 WL 3261252 (D.N.J. Sept. 30, 2009) for the proposition that “it is not unusual for crystal forms [to] share peaks in the same location of an x-ray pattern.” (Apotex Br. at 26.) Apotex, however, neglected to mention that in that case the court was trying to determine whether a *sole* peak is determinative of whether the compound is in crystalline form. *See Roche*, at *6-8. *Roche* is inapposite to this case because claim 1 of the ‘725 patent requires that the claimed compound is “substantially in accordance” with FIG. 1, not a single peak.

Accordingly, BMS respectfully submits that the Court should reject Apotex’s proposed construction and adopt BMS’s construction.

- D. “which is characterized by an x-ray powder diffraction pattern (Cu k_{α} γ =1.5418 Å at a temperature of about 23° C.) comprising four or more 2 θ values selected from the group consisting of: 18.0±0.2, 18.4±0.2, 19.2±0.2, 19.6±0.2, 21.2±0.2, 24.5±0.2, 25.9±0.2, and 28.0±0.2”**

This phrase appears in claim 3. BMS’s proposed construction is “[w]hich is characterized by XRPD pattern taken with Cu k_{α} λ =1.5418 Å at a temperature of about 23° C, having at least four 2 θ values selected from the group consisting of: 18.0±0.2, 18.4±0.2, 19.2±0.2, 19.6±0.2, 21.2±0.2, 24.5±0.2, 25.9±0.2, and 28.0±0.2.”

Apotex contends that this claim language is insolubly ambiguous. However, Apotex’s position is supported only by attorney argument. Its expert Dr. Desiraju testified that he was not asked to opine about claim 3. (Gannon Cert. II Ex. D, Desiraju Dep. 45:20-21; 90:6-91:3.) Apotex provided four attorney arguments in support of its position. First, it reiterates its flawed reasoning for limiting the crystalline monohydrate to the process conditions. (Apotex Br. at 27.) As stated above in II.A, Apotex’s own expert does not support this position. Second, Apotex states that the language “selected from the group consisting of” “requires the presence of just these few peaks and no others.” (Apotex Br. at 28.) However, claim 3 specifically states that the X-ray diffraction pattern “*comprising four or more* 2 θ values selected from the group consisting of” the list of recited values. (Emphasis added.) There is nothing in the specification or the claim language that would exclude the presence of other peaks. Third, Apotex erroneously argues that the XRPD peaks are not tethered to the crystalline monohydrate of formula (IV). The preamble of claim 3 unambiguously states that it is the “crystalline monohydrate of the compound of formula (IV)” which is characterized by an X-ray diffraction pattern comprising the recited peaks. Lastly, Apotex protests the variance of ±0.2 for the 2 θ values in the claim as being overly broad and unsupported by the specification. However, Dr.

Desiraju confirmed that ± 0.2 deviation was commonly used by individuals of ordinary skill. (Gannon Cert. II Ex. D, Desiraju Dep. 96:22-97:4.).

Moreover, Apotex's reliance on *Abbott Labs. v. Sandoz, Inc.*, 486 F. Supp. 2d 767 (N.D. Ill. 2007) is misplaced. In *Abbott*, the Court resorted to extrinsic evidence to construe "about" because the specification did not set forth the range of the diffraction angles. *Id.* at 770, 772-73. In stark contrast, claim 3 specifically sets forth a ± 0.2 deviation for each value.

Accordingly, BMS respectfully submits that the Court should reject Apotex's indefiniteness argument and adopt BMS's proposed construction.

**E. "characterized by unit cell parameters approximately equal to the following:
Cell dimensions: $a(\text{\AA})=13.8632(7)$; $b(\text{\AA})=9.3307(3)$; $c(\text{\AA})=38.390(2)$;
Volume= $4965.9(4) \text{\AA}^3$
Space group Pbcu
Molecules/unit cell 8
Density (calculated) (g/cm^3) 1.354"**

This phrase appears in claim 5. BMS's proposed construction is "[p]lain meaning as understood by a person of ordinary skill in the art." (BMS Br. at 25.) Apotex argues that the term "approximately equal" is indefinite. However, the term "approximately" is a descriptive term commonly used in patent claims to "avoid a strict numerical boundary to the specified parameter" and these terms have been repeatedly found by the courts to be definite. *See, e.g., Ecolab, Inc. v. Envirochem, Inc.*, 264 F.3d 1358, 1367 (Fed. Cir. 2001) (quoting *Pall Corp. v. Micron Seps.*, 66 F.3d 1211, 1217 (Fed. Cir. 1995)); *Andrew Corp. v. Gabriel Elecs. Inc.*, 847 F.2d 819, 821-22 (Fed. Cir. 1988) (noting that terms such as "substantially equal" and "closely approximate" are ubiquitously used in patent claims, and that such use has been accepted in patent application examination and upheld by the courts).

Apotex relies on Dr. Desiraju for its indefiniteness argument. However, Dr. Desiraju's objection was based purely on semantics as he objected only to the use of "equal" in connection

with “approximately,” but asserted that use of the term “approximately the same” instead would be meaningful. (Gannon Cert. II Ex. D, Desiraju Dep. 107:2- 108:16.)

Relying solely on attorney argument, Apotex further contends that unit cell parameters listed in claim 5 could not be obtained by BMS because the crystalline monohydrate of the compound of formula (IV) of claim 5 has to be in powder form based on the XRPD 2 θ values listed in claim 3, the claim from which claim 5 depends. However, Apotex’s argument is contradicted by its own expert. Dr. Desiraju testified that the unit cell parameters recited in claim 5 are generated from the X-ray diffraction pattern obtained from a single crystal experiment. (*Id.* at 111:13-19.) Accordingly, Apotex’s indefiniteness argument should be rejected.

F. “which is characterized by differential scanning calorimetry thermogram and a thermogravimetric analysis substantially in accordance with that shown in FIG. 2” (Claim 2)

“being further characterized by a differential scanning calorimetry having a broad peak between approximately 95° C and 130° C” (Claims 9 and 12)

“wherein the differential scanning calorimetry further has a peak at approximately 287° C” (Claim 11)

BMS’s proposed constructions are set forth in its opening brief. (BMS Br. at 23, 27, 30.) Instead of proffering claim constructions for the above three terms, Apotex asserts that these terms are insolubly ambiguous. (Apotex Br. at 30-33.) Apotex is wrong.

First, relying on attorney argument, Apotex contends that the ‘725 patent does not provide the measurement protocols for the DSC studies used to obtain the data depicted in FIG. 2 and recited in the claim terms at issue. (*Id.* at 30.) This contention is incorrect. The ‘725 patent discloses in detail the experimental conditions that were used to conduct the DSC analysis, *e.g.*, the experiment was performed in an open aluminum DSC pan, rate of heating was 10°C per

minute in the temperature range between 25° and 350° C. (*See* Atwood Ex. A, col. 43, ll. 1-22; Atwood ¶ 41.). Indeed, Apotex’s position is again contradicted by its own expert. Dr. Desiraju testified that the description of the measurement protocols in the ‘725 patent was sufficient for one of ordinary skill in the art to conduct the disclosed DSC and thermogravimetric analyses. (Gannon Cert. II Ex. D, Desiraju Dep. 105:6-106:2.)

Second, Apotex argues that the term “which is characterized by differential scanning calorimetry thermogram and a thermogravimetric analysis substantially in accordance in accordance with that shown in FIG. 2” in claim 2 is indefinite. (Apotex Br. at 31-32.) However, Apotex has previously offered a construction for this term in the parties’ Joint Claim Construction and Prehearing Statement. Apotex asserted then that this term means “[t]he product being characterized *must match* both the differential scanning calorimetry thermogram and the thermogravimetric results presented in FIG. 2 of the patent specification....” (Dkt. 51, Ex. B at 36.) (Emphasis added.) Apotex apparently has now retreated from that proposed construction. This is not surprising given that Dr. Desiraju testified that “substantially in accordance” does not mean “must match.” (Gannon Cert. II Ex. D, Desiraju Dep. 99:2-8.) Moreover, Dr. Desiraju agrees with BMS’s position that there are measurement errors associated with DSC and TGA experiments. (*Id.* at 99:9-25.) In fact, Dr. Desiraju testified that samples of the *same* crystalline material can result in different DSC and TGA patterns due to measurement errors. (*Id.* at 102:7-16; 103:21-25.) Accordingly, since there is no support whatsoever for Apotex’s proposed “must match” construction, the Court should adopt BMS’s proposed construction which is fully supported not only by the intrinsic evidence, but also by both parties’ experts. (BMS Br. at 22-24.)

Third, Apotex claims that BMS is attempting to improperly expand the scope of its claims to cover other substances, such as other hydrates, other compounds, and other excipients. (Apotex Br. at 31.) This argument is unfounded and is directly contradicted by the claim language. The claims at issue are explicitly limited to “the crystalline monohydrate of the compound of formula (IV).”

Fourth, Apotex objects to the use of the term “peak” to refer to the thermal events in a DSC trace on the ground that a person of ordinary skill in the art would not understand the meaning of “peak.” (Apotex Br. at 32.) Again, Apotex’s argument holds no water. As Dr. Atwood discussed in his Declaration, the term “peak” is used throughout the art. (Atwood ¶ 42.) Further, Apotex’s own expert Dr. Desiraju testified that in the context of the ‘725 patent he understood the meaning of “peak” and that he and others regularly use the term “peak” in connection with describing DCS and TGA traces. (Gannon Cert. II Ex. D, Desiraju Dep. 117:10-119:24; 122:2-124:22.) Indeed, Dr. Desiraju understood that the peak at approximately 287° C recited in claim 11 corresponds to the melting point of the dehydrated compound, as stated in BMS’s proposed construction. (*Id.* at 123:21-124:6.)

Finally, Apotex argues that the term “broad peak” and “approximately” are “words of degree” and are insolubly ambiguous. (Apotex Br. at 32-33.) This argument is again contradicted by Apotex’s own expert Dr. Desiraju. Dr. Desiraju testified that in the context of the ‘725 patent he understood that the “broad peak between approximately 95° C and 130° C” corresponds to the loss of one water of hydration. (Gannon Cert. II Ex. D, Desiraju Dep. 119:8-24; 125:10-22.) He further testified that there are errors associated with DSC, TGA, and melting point measurements and the use of “approximately” is appropriate in such context. (*Id.* at 99:9-25; 124:7-22.)

For all of the forgoing reasons, Apotex's indefiniteness arguments should be rejected.

G. “which corresponds to the loss of one water of hydration on thermogravimetric analysis”

This phrase appears in claims 9 and 12. BMS's proposed construction is “[w]hich corresponds to a weight loss attributable to one water of hydration on thermogravimetric analysis.” (Apotex Br. 28.) Apotex argues that this claim term is insolubly ambiguous because “it calls for the use of the test method to measure the ‘loss of one water of hydration on thermogravimetric analysis,’ which is not the output of the test method.” (*Id.* at 33.) Apotex's argument is flawed. The claim term does not require that TGA is used to determine one water of hydration was lost, only that the broad peak between 95° C and 130° C corresponds to a weight loss attributable to one water of hydration on thermogravimetric analysis. As conceded by Dr. Desiraju, in the context of the ‘725 patent, a person of ordinary skill in the art would understand that the broad peak between 95° C and 130° C corresponds to a weight loss attributable to one water of hydration on thermogravimetric analysis. (Gannon Cert. II Ex. D, Desiraju Dep. 119:8-24; 125:10-22.)

Relying only on attorney argument, Apotex also states that the “compound of claim 3” does not have a water molecule to lose because it is the compound of formula (IV), *i.e.*, it is not the monohydrate. (Apotex Br. at 33-34.) As Dr. Atwood explained in his declaration, “one of ordinary skill in the art would understand that the ‘compound’ in these phrases refers to the crystalline monohydrate of the compound of formula (IV).” (Atwood ¶ 47.) This understanding is supported by the specification of the ‘725 patent. (*Id.* at ¶¶ 47-51.) Indeed, Dr. Desiraju understood the meaning of this term and FIG. 2 of the ‘725 patent which illustrated the DSC and TGA thermograms of the crystalline monohydrate of the compound of formula (IV). (Gannon

Cert. II Ex. D, Desiraju Dep. 60:25-61:6; 66:25-69:14; 118:1-119:24.) Apotex's indefiniteness argument has no merit and should be rejected.

H. “which is further characterized by a weight loss of 3.48% by thermogravimetric analysis between 50° C and 175° C”

This phrase appears in claim 10. BMS's proposed construction is “[w]hich is further characterized by a weight loss of 3.48% by thermogravimetric analysis between 50° C and 175° C, taking into account variations due to measurement errors and dependent upon the measurement conditions employed.” (BMS Br. at 29.)

Apotex does not offer a construction for this claim term, but only argues that it is insolubly ambiguous based on its unfounded restriction of “compound” to the compound formula (IV), *i.e.*, “compound” is not referring to the monohydrate. (Apotex Br. at 34.) As stated above, a person of ordinary skill in the art would understand the term “compound of claim ___” as referring to the crystalline monohydrate of the compound of formula (IV). Further, Dr. Desiraju testified that he understood that the 3.48 % weight loss corresponds to the loss of one water of hydration *from the monohydrate*. (Gannon Cert. II Ex. D, Desiraju Dep. 68:7-69:8.) Dr. Desiraju further agreed that there are measurement errors associated with TGA analysis. (*Id.* at 99:9-25.) Thus, BMS respectfully submits that the Court reject Apotex's indefiniteness argument and adopt BMS's proposed construction.

I. “The compound of claim 1” or “The compound of claim 3” or “The compound of claim 9” or “The compound of claim 12”

This phrase appears in claims 2, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15 and 16. BMS's proposed construction is “[p]lain meaning as understood by a person of ordinary skill in the art, *i.e.*, the crystalline monohydrate of the compound of formula (IV).”

Based only on attorney argument, Apotex argues that the “compound of claim ___” is restricted to the “compound” of formula (IV), *i.e.*, “compound” is not referring to the

monohydrate. (Apotex Br. at 35-36.) As explained by Dr. Atwood, the phrase “the compound of claim ___” is referring to the crystalline monohydrate of the compound of formula (IV).

(Atwood ¶¶ 47-51; BMS Br. at 21-22.) Accordingly, Apotex’s proposed construction should be rejected.

J. “A process for preparing the compound of claim 3”

This claim term appears in claims 6 and 7. BMS’s proposed construction is “[p]lain meaning as understood by a person of ordinary skill in the art, *i.e.*, a process for preparing the crystalline monohydrate of the compound of formula.” Apotex does not offer a construction for this claim term, but instead, argues that the claimed process must occur in the United States.

(Apotex Br. at 34-35.) This argument has nothing to do with claim construction. Indeed, there is nothing in the intrinsic evidence that restricts the process to one occurring in the United States.

Further, Apotex’s argument is contrary to statute. 35 U.S.C. § 271(g) states that it is an act of infringement to import into the United States a product which is made by a process patented in the United States. Thus, a product made by a process practiced abroad can infringe a U.S. patent.

IV. CONCLUSION

For the reasons discussed above, BMS respectfully requests that the Court adopt its proposed constructions.

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Respectfully submitted,

s/Liza M. Walsh

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